



# Drug-gene interactions and the search for missing heritability: a cross-sectional pharmacogenomics study of the QT interval

## Citation

Avery, C. L., C. M. Sitlani, D. E. Arking, D. K. Arnett, J. C. Bis, E. Boerwinkle, B. M. Buckley, et al. 2013. "Drug-gene interactions and the search for missing heritability: a cross-sectional pharmacogenomics study of the QT interval." *The pharmacogenomics journal* 14 (1): 6-13. doi:10.1038/tpj.2013.4. <http://dx.doi.org/10.1038/tpj.2013.4>.

## Published Version

doi:10.1038/tpj.2013.4

## Permanent link

<http://nrs.harvard.edu/urn-3:HUL.InstRepos:12785812>

## Terms of Use

This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA>

## Share Your Story

The Harvard community has made this article openly available.  
Please share how this access benefits you. [Submit a story](#).

[Accessibility](#)

Published in final edited form as:

*Pharmacogenomics J.* 2014 February ; 14(1): 6–13. doi:10.1038/tpj.2013.4.

## Drug-gene interactions and the search for missing heritability: a cross-sectional pharmacogenomics study of the QT interval

*A full list of authors and affiliations appears at the end of the article.*

### Abstract

Variability in response to drug use is common and heritable, suggesting that genome-wide pharmacogenomics studies may help explain the “missing heritability” of complex traits. Here, we describe four independent analyses in 33,781 participants of European ancestry from ten cohorts that were designed to identify genetic variants modifying the effects of drugs on QT interval duration (QT). Each analysis cross-sectionally examined four therapeutic classes: thiazide diuretics (prevalence of use=13.0%), tri/tetracyclic antidepressants (2.6%), sulfonylurea hypoglycemic agents (2.9%), and QT prolonging drugs as classified by the University of Arizona Center for Education and Research on Therapeutics (4.4%). Drug-gene interactions were estimated using covariable adjusted linear regression and results were combined with fixed-effects meta-analysis. Although drug-SNP interactions were biologically plausible and variables were well-measured, findings from the four cross-sectional meta-analyses were null ( $P_{\text{interaction}} > 5.0 \times 10^{-8}$ ). Simulations suggested that additional efforts, including longitudinal modeling to increase statistical power, are likely needed to identify potentially important pharmacogenomic effects.

### Keywords

QT interval; pharmacogenomics; gene-environment interaction

## INTRODUCTION

The role of inheritance in response to drug exposure has long been appreciated, dating to as early as 1932 when the inability to taste phenylthiocarbamide was demonstrated to follow an autosomal recessive inheritance pattern.<sup>1</sup> Today, the promise of pharmacogenomics lies in its potential to tailor drug prescription and dosing to individual patients,<sup>2–4</sup> a practice exemplified by the use of a patient’s genotype to inform warfarin dosing,<sup>5, 6</sup> to avoid anemia during hepatitis C treatment,<sup>7</sup> or to predict benefit from and therefore guide chemotherapy in breast cancer.<sup>8</sup> Documented heterogeneity of drug response has also prompted the suggestion that examining drug-gene interactions may help explain a notable proportion of the heritability for complex traits that remains unexplained by genome wide association (GWA) studies.<sup>9, 10</sup> Yet to date, large scale pharmacogenomics studies are few in number.<sup>11</sup>

Users may view, print, copy, download and text and data- mine the content in such documents, for the purposes of academic research, subject always to the full Conditions of use: [http://www.nature.com/authors/editorial\\_policies/license.html#terms](http://www.nature.com/authors/editorial_policies/license.html#terms)

Corresponding Author: Christy Avery, Department of Epidemiology, University of North Carolina Chapel Hill, Bank of America Center, 137 E. Franklin St., Suite 306, Chapel Hill, NC 27514, (919) 966-4312 (voice), (919) 966-9800 (fax), [christy\\_avery@unc.edu](mailto:christy_avery@unc.edu).

### CONFLICT OF INTEREST

Conflicts of Interest and Source of Funding  
The authors have no conflicts to disclose.

The duration of the QT interval (QT), a non-invasive measure of the ventricular action potential estimated from the resting, standard twelve-lead electrocardiogram (ECG), offers a good model for examining the value of pharmacogenomics. In addition to being well-measured,<sup>12</sup> heritable,<sup>13, 14</sup> and heterogeneous among those exposed to what are now called “QT-prolonging drugs”,<sup>15</sup> QT prolongation is the most common cause of withdrawal or restricted marketing of pharmaceuticals<sup>16</sup> largely because of its established association with ventricular tachyarrhythmia,<sup>17</sup> sudden cardiac death, and all-cause mortality.<sup>18, 19, 20</sup> However, prospectively identifying subpopulations at risk for drug-induced QT prolongation and its sequelae remains a challenge.<sup>16</sup>

Although heritability estimates suggest a substantial genetic component underlying QT, genetic variation at the 26 single nucleotide polymorphisms (SNPs) identified to date by GWA studies together explain approximately 5–8% of the variance in QT.<sup>21–27</sup> Popular explanations for this missing heritability include rare variants that are poorly represented on commercial genotyping arrays as well as gene-gene and gene-environment interactions.<sup>10</sup> In search of this missing heritability, we assessed pharmacogenomic influences on QT by conducting four cross-sectional GWA analyses in ten populations of European ancestry. The goal of the studies was to identify genetic variants modifying the association between drugs in four therapeutic classes previously associated with QT prolongation or sudden death<sup>28–32</sup> and the duration of QT.

## METHODS

### Study populations

A meta-analysis of ten cohorts with GWA data that included 33,781 participants of European descent was performed to investigate cross-sectional drug-SNP interactions in QT. Five cohorts were from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium:<sup>33</sup> the Age, Gene/Environment Susceptibility – Reykjavik Study (AGES), the Atherosclerosis Risk in Communities study (ARIC), the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS), and the Rotterdam Study (RS). Since the inception of CHARGE, five additional cohorts have joined the effort: the Erasmus Rucphen Family study (ERF), Health 2000, the Health Aging, Body and Composition (Health ABC) study, the Multi-Ethnic Study of Atherosclerosis (MESA), and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). At baseline for all cohorts, drug exposure was queried and participants underwent standardized ECGs, which were read for QT duration. Each cohort followed a pre-specified analysis protocol and findings from the within-cohort analyses were then combined by meta-analysis. All studies were approved by local ethics committees and all participants provided written informed consent. Additional information on the participating studies is provided in the Supplementary Material.

### Study design; inclusion and exclusion criteria

Within each cohort, we performed four separate cross-sectional analyses using drug, covariate, and ECG data collected at the baseline examination. Participants with the following characteristics were excluded from the analysis: poor quality ECG, extreme QRS duration prolongation including that due to bundle branch block (QRS > 120 ms), atrial fibrillation/flutter on ECG, paced rhythm, or second or third degree atrioventricular block. Heart failure at study baseline was an additional exclusion for the thiazide diuretic, sulfonylurea hypoglycemic agent, and tri/tetracyclic antidepressant analyses. Users of loop diuretics, regardless of thiazide use, also were excluded from analyses examining thiazide diuretics.

## Definition of drug exposure

Drug use was assessed by method of medication inventory or pharmacy database (Supplemental Table 1). Six of the nine cohorts using the medication inventory method captured medications used within one to two weeks preceding ECG assessment. The remaining three cohorts currently using medication inventory methods assessed medications used on the day of ECG recording. The Rotterdam Study was the only cohort that assessed drug exposure via pharmacy databases; investigators classified a participant as exposed if he/she filled a prescription for a drug class of interest within 30 days preceding the ECG recording.

Four classes of therapeutic drugs previously associated with QT prolongation were examined: thiazide diuretics,<sup>30, 32</sup> tri/tetracyclic antidepressants,<sup>31</sup> sulfonylurea hypoglycemic agents,<sup>29</sup> and University of Arizona Center for Education and Research on Therapeutics (UAZ CERT)-classified QT prolonging drugs.<sup>28</sup> Participants were classified: as thiazide users if they took a thiazide or thiazide-like diuretic in a single or combination preparation, with or without potassium sparing diuretic or potassium supplements; as sulfonylurea users if they took a first or second generation sulfonylurea anti-diabetic; and as tri/tetracyclic users if they took a tricyclic or tetracyclic antidepressant, ignoring concomitant use of other therapeutic drug classes.

The UAZ CERT classification was used to group medications into four classes based on the likelihood of QT-prolongation: definite, possible, conditional, or no/unknown. Participants using two or more drugs classified as conditional were reclassified as possible. When participants took drugs from more than one UAZ CERT class, the highest class was assigned. For the UAZ CERT analyses, participants classified as users of definite or possible QT prolonging drugs were classified as exposed; participants classified as no/unknown were classified as unexposed; and those reporting use of one conditional QT prolonging agent were excluded.

## QT measurement

For each study, technicians digitally recorded resting, supine (or semi-recumbent), standard twelve-lead ECGs for each participant (Supplementary Table 2) on the same day drug exposure was recorded. Studies used comparable procedures for preparing participants, placing electrodes, recording, transmitting, processing and controlling quality of the ECGs, although QT in the various studies was measured by different automated systems and therefore will be subject to a small variation equivalent to inter observer error. The ECG from the baseline visit was selected when multiple ECGs were available.

## Genotype arrays and imputation

Genome-wide SNP genotyping was performed within each cohort using either the Affymetrix or Illumina genotyping arrays (Supplemental Table 3). Gender mismatches and duplicate samples were excluded. First-degree relatives were excluded in all cohorts except the family-based FHS and ERF, which accounted for relatedness in the association analysis. DNA samples with genotyping success rates between <95% and <99%, depending on the cohort, were excluded. SNPs also were excluded when genotyping call rate thresholds were between 95% and 99%, and minor allele frequencies (MAF) < 1%, the determination of which was cohort-specific.

To increase coverage and facilitate evaluation of the same SNPs across cohorts, genotypes were imputed using BIMBAM,<sup>34</sup> MACH<sup>35</sup> or BEAGLE,<sup>36</sup> which applied algorithms that inferred unobserved genotypes in a probabilistic manner. Imputation was performed for ~2.5

million autosomal SNPs based on the HapMap Phase 2 (build 36) CEU reference population (Supplemental Table 3).

### Statistical analysis

Each cohort performed four GWA analyses of QT across approximately 2.5 million SNPs comparing drug users to non-users. Study designs that restricted to those on treatment were not chosen because of the large potential for type I error due to the inseparability of the SNP main effect and interaction effect estimates.<sup>37</sup> Each drug-genotype interaction was estimated using linear regression, under an additive genetic model, and using robust standard errors except in the family-based FHS and ERF cohorts, which used linear mixed-effects models as implemented in the GWAF package for R (FHS)<sup>38</sup> and GenABEL/ProbABEL (ERF).<sup>39, 40</sup> All regressions adjusted for the following covariates: age (year), sex, RR interval (ms), recruitment site when appropriate, and principal components summarizing participants' global genetic ancestry to account for confounding by race/ethnicity. Additionally, the four-category UAZ CERT drug categorization was included as a nominal covariate in the thiazides, sulfonylureas, and tri/tetracyclic analyses.

For some SNPs, the numbers of genetic variants among participants on drug therapy were too small to permit use of standard asymptotic results. Therefore, cohort-specific inference used a (Student's) *t* as the reference distribution. The degrees of freedom for the *t* reference distribution were calculated as the cohort- and SNP-specific product of: the number of drug-exposed participants, the SNP imputation quality (range: 0, 1), and the MAF (range: 0, 0.50). For each SNP, cohort-specific *P*-values were calculated by comparing  $\beta$ /standard error estimates to this reference, with the resulting *P*-values then meta-analyzed using the standard weighted Z-statistic method,<sup>41</sup> with weights based on the number exposed to the drug multiplied by the SNP imputation quality.

Cohort-specific results were corrected by their respective genomic inflation factors ( $\lambda_s$ ).<sup>42</sup> The genome-wide threshold for significant drug-SNP interaction was  $P < 5.0 \times 10^{-8}$ . The software packages R, ProbABEL, GenABEL, PLINK, and GRIMP were used to estimate cohort-specific results (Supplemental Table 3) and METAL<sup>41</sup> was used to generate summary meta-analytic estimates of the drug-SNP interaction parameters. Quantile-quantile (Q-Q) plots were used to identify systematic miscalibration of the test statistic for the drug-genotype interactions.

### Statistical power simulations

Power to detect drug-SNP interactions using cross-sectional and longitudinal modeling approaches was estimated via simulation studies. Assumptions, which were informed by study data, included: (1) 20,000–30,000 participants, (2) a two-sided, per-SNP  $\alpha = 5.0 \times 10^{-8}$ , (3) a mean heart-rate corrected QT (standard deviation) = 426 (20) ms, (4) a prevalence of drug exposure = 0.10 for the longitudinal simulations and 0.03–0.14 for the cross-sectional simulations, (5) a mean drug effect for those with zero copies of the minor allele = 1 ms, (6) a mean SNP effect for those not exposed to drug = 1, (7) a MAF = 0.20 for the longitudinal simulations and MAF 0.05–0.30 for the cross-sectional simulations, and (8) an additive model of inheritance. The drug-SNP interaction effect was varied in size. To evaluate the power that could be gained by incorporating repeated measures over time, the simulation incorporated up to 2–6 measurements of QT duration and drug exposure for each participant, and the within-person correlation in QT was set at 0.5 based on unpublished observations. Drug use was either temporally constant or variable. When variable, drug exposure was assumed to be completely random at each time. An attrition rate of 5% per visit, plus random missingness of 5% of remaining measurements, was assumed. Linear models with robust standard errors were used for cross-sectional analyses, and generalized

estimating equations (GEE) with exchangeable working correlation were used for longitudinal analyses.

## RESULTS

GWA analyses were performed to examine whether common genetic variants modified the effects of exposure to drugs in four therapeutic classes on QT. The ten participating cohorts of European descent varied in size (range: 1,435 – 8,132, Table 1). On average, participants were predominantly female (percent female range: 49.4%–62.5%) and middle-aged to elderly (mean age range = 40–75 years). The estimated prevalence of drug exposure at study baseline was highest for thiazides (13.6%), lowest for the tri/tetracyclics (2.6%), and intermediate for the sulfonylurea hypoglycemic agents (2.9%) and UAZ CERT-classified QT-prolonging drugs (4.4%). After applying genotyping and imputation quality control measures, a total of approximately 2.5 million autosomal SNPs were available for analysis.

Quantile-quantile plots based on meta-analyses of the cohort-specific, drug-SNP interaction test statistics revealed moderately conservative distributions, as demonstrated by  $\lambda < 1.0$  (range: 0.89–0.99) and slightly earlier departure of *P*-values in the direction of conservatism, compared to what would have been expected by chance alone (Figure 1). In line with statistical theory, overstated significance due to miscalibration, which was common using standard asymptotic methods, was not observed using the t-reference approach. These patterns did not differ by the prevalence of medication use at study baseline.

No genome-wide significant cross-sectional interactions ( $P < 5.0 \times 10^{-8}$ ) were detected for any of the four drug classes (Figure 2). The top five loci (Supplemental Table 4) also were inconsistent across drug classes. Cross-sectional meta-analyses restricted to the 26 SNPs reported by previously published GWA studies of QT main effects were similarly null (interaction  $P = 0.01$ , Table 2), as were results for SNPs reported by recent pharmacogenomic studies of QT and drug-induced QT prolongation (Supplemental Table 5).<sup>43–47</sup>

### Statistical power

Given the robustly null results and because four cohorts (52.2% of total sample size) had repeated ECG recordings and drug exposure assessments (range: 2, 10; Supplemental Table 2), we examined statistical power for the cross-sectional analysis and the degree to which analyses incorporating repeated measures would increase statistical power. Simulations demonstrated that all cross-sectional analyses were underpowered, especially for drug categories with 3% prevalence (Supplemental Figure 1). However, when the prevalence of drug use increased to 14% (e.g. thiazides) and the SNP was common, we achieved 80% power to detect an effect of 3.25 ms. Incorporating repeat ECG measures with constant drug exposure yielded a moderate increase in statistical power, although the greatest increase was associated with a time-varying drug exposure, i.e. observed QT measurement on and off drug within an individual (Figure 3). For example, we had > 80% power to detect interactive drug-SNP effects less than 2 ms when a time-varying drug exposure was examined at least four different times.

## DISCUSSION

In this study composed of approximately 35,000 participants of European descent from ten cohorts, we examined cross-sectional evidence for drug-SNP interactions influencing QT. We did not identify any variants that significantly modified the association between QT and drugs in four therapeutic classes previously associated with QT prolongation. An analysis limited to SNPs with previously identified genome-wide significant main effects yielded



similarly null results, as did one restricted to recent pharmacogenomic studies of QT and drug-induced QT prolongation.<sup>43–47</sup>

It remains unclear how much “missing heritability” future gene-environment interaction studies will explain, as GWA studies of interaction effects are only beginning to emerge. Drug exposure likely represents a good candidate for gene-environment interrogation, as medication use is highly prevalent<sup>48, 49</sup> and pharmacogenomics is one of the few fields in which gene-environment interactions have been consistently replicated across studies.<sup>50–54</sup> It is also biologically plausible that the human genome contains variants that modify the association between drug exposure and phenotype, as such common variant alleles would have emerged long before the appearance of modern pharmacotherapies.<sup>55</sup>

We chose a well-measured phenotype<sup>12</sup> with biologically plausible pharmacogenomic effects<sup>15</sup> and our drug assessment methods were sensitive and reliable,<sup>56, 57</sup> yet were unable to detect any genome-wide significant interactions. One possible explanation is statistical power. Using stringent genome-wide significance thresholds, we remained underpowered to detect cross-sectional interactions below six ms for low prevalence drugs (e.g. the sulfonylurea hypoglycemic agents, UAZ CERT, and tri/tetracyclic antidepressants analyses). Although 80% power is achieved when a more common drug exposure is examined (e.g. thiazides), three ms is outside the range of typical genetic effects observed for QT.

Statistical power remains a challenge in gene-environment interaction studies, although the potential utility of longitudinal models to increase power has been shown here and described previously.<sup>58</sup> Increases in power from longitudinal models are due in part to increased precision in outcome measurement; but when exposure varies over time, power increases are also due to within-person comparisons of the outcome under each drug status. Therefore, longitudinal analyses increase power more than expanding sample sizes when there is variability in exposure over time and minimal concern about time-dependent confounding that would complicate the interpretation of longitudinal estimates. Analyses of drug-gene interaction effects on QT satisfy both conditions. However, longitudinal models remain rare in GWA studies examining both main and interactive effects and likely reflect the considerable computational complexities associated with implementing a longitudinal model that accommodates the scale of a typical GWA study. We are currently developing methods to implement longitudinal analyses on a genome-wide scale and future work will include re-evaluation of gene-drug interactions on QT interval using available longitudinal data.

In addition to performing a GWA study of QT-prolonging drug use and QT, as a sensitivity analysis we separately evaluated 26 SNPs previously associated with QT main effects. Restricting interaction analyses to SNPs with replicated main effects is not uncommon in GWA interaction studies,<sup>59</sup> and likely reflects statistical power concerns given the stringent GWA study significance thresholds. Here, we demonstrated that none of the previously identified QT SNPs modified the association between QT prolonging drug use and QT. This is not surprising, as SNPs selected on the basis of an extreme *P*-value for a single main effect may be less likely to harbor heterogeneity across population subgroups.

Several limitations of the present study warrant consideration to inform future efforts examining pharmacogenomic influences on QT. First, we did not address the potential for bias related to duration of use. It is difficult to gauge the overall influence of duration of use effects, in which participants taking the drugs for years or decades are those least likely to have experienced side effects, as they likely differ by drug class. For example, intraclass correlation coefficients (ICC) estimated in the ARIC study suggest intermittent patterns of use for the UAZ CERT class (ICC = 0.39), but long-term usage patterns for thiazide diuretics (ICC = 0.69). Although we can suppose that drugs with intermittent patterns of use are less

influenced by selection bias related to duration of use than those characterized by long-term usage patterns, further studies examining the robustness of pharmacogenomic findings to such biases are clearly warranted. Second, confounding by contraindication also could result from the comorbidities that influence drug use and QT. However, previous simulations indicated that confounding by contraindication has very modest effects on estimates of interaction in pharmacogenomic studies.<sup>37</sup> Third, our results are statistically conservative, given the evidence of under-statement of significance for the drug-SNP interaction estimates suggested by QQ plots. However, it is unlikely that the bias would be so large as to cause truly genome-significant loci to be reclassified as non-significant. Fourth, we relied on medication inventory and pharmacy data to ascertain medication usage. Although neither source of information guarantees exposure, validation studies suggest good agreement between serum drug concentrations and several (e.g. thiazide diuretic) exposures ascertained by medication inventory.<sup>56</sup> Pharmacy data appear to be even more accurate in this regard.<sup>60</sup>

Finally, the drug classes considered herein, particularly the UAZ CERT class, combine QT-prolonging drugs that may have heterogeneous mechanisms of action, thereby reducing the sensitivity for detecting SNPs possessing important, population-level interactive effects. However, disagreement among classifications is much lower in the highest ventricular arrhythmia risk category<sup>16</sup> and for older drugs, including the majority of those taken by participants at the time of their past examinations. Relatively systematic attempts to exhaustively identify, classify, and update current lists of QT-prolonging medications in pharmacologically more meaningful ways are also unavailable. Moreover, nearly all drugs that prolong QT and cause ventricular arrhythmias inhibit the rapidly activating delayed rectifier potassium current.<sup>16, 61</sup>

In conclusion, our findings suggest that additional efforts are required to realize the potential of pharmacogenomics. In addition to careful selection of the phenotype of interest, researchers interested in pharmacogenomics should increase the number of measures per participant and invest in longitudinal modeling infrastructure scalable to GWA studies to help increase statistical power. Although these cross-sectional analyses do not support strong drug-gene interactions for QT, future efforts incorporating longitudinal modeling are needed to determine whether the reported associations are underpowered or genuinely null.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Authors

Christy L. Avery, PhD, Colleen M. Sitlani, PhD, Dan E. Arking, PhD, Donna K. Arnett, PhD, Joshua C. Bis, PhD, Eric Boerwinkle, PhD, Brendan M. Buckley, DPhil, Y.-D. Ida Chen, PhD, Anton JM de Craen, MSc, PhD, Mark Eijgelsheim, MD, PhD, Daniel Enquobahrie, MD, PhD, Daniel S. Evans, PhD, Ian Ford, PhD, Melissa E. Garcia, MPH, Vilundur Gudnason, MD, PhD, Tamara B. Harris, MD, MS, Susan R. Heckbert, MD, PhD, Hagit Hochner, PhD, Albert Hofman, MD, Wen-Chi Hsueh, MPH, PhD, Aaron Isaacs, PhD, J. Wouter Jukema, MD, PhD, Paul Knekt, PhD, Jan A. Kors, PhD, Bouwe P. Krijthe, MSc, Kati Kristiansson, PhD, Maarit Laaksonen, PhD, Yongmei Liu, MD, PhD, Xiaohui Li, MD, MS, Peter W. MacFarlane, PhD, DSc, Christopher Newton-Cheh, MD, MPH, Markku S. Nieminen, PhD, Ben A. Oostra, PhD, Gina M. Peloso, PhD, Kimmo Porthan, MD, Kenneth Rice, PhD, Fernando F. Rivadeneira, MD, PhD, Jerome I. Rotter, MD, Veikko Salomaa, MD, PhD, Naveed Sattar, MD, PhD, David S. Siscovick, MD, MPH, P. Eline Slagboom, PhD, Albert V. Smith, PhD, Nona Sotoodehnia, MD, David J. Stott, MD, PhD, Bruno H. Stricker,



MD, PhD, Til Stürmer, MD, PhD, Stella Trompet, MSc, PhD, Andre G. Uitterlinden, PhD, Cornelia M. van Duijn, PhD, Rudi GJ Westendorp, MD, PhD, Jacqueline C. Witteman, PhD, Eric A. Whitsel, MD, MPH, and Bruce M. Psaty, MD, PhD Departments of Epidemiology (CLA, TS, EAW), and Medicine (EAW), the University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; Departments of Medicine (BMP), Health Services (BMP), Epidemiology (SRH, BMP, DSS) Cardiovascular Health Research Unit (CMS, SRH, BMP, DSS, JB, DE, HH) and Division of Cardiology (NS), University of Washington, Seattle, Washington, USA; Group Health Research Institute, Group Health Cooperative, Seattle, Washington, USA (BMP); Department of Epidemiology, University of Alabama Birmingham, Birmingham, Alabama, USA (DKA); McKusick-Nathans Institute of Genetic Medicine and Department of Medicine, Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA (DEA); Division of Epidemiology and Center for Human Genetics, The University of Texas Health Science Center, Houston Texas, USA (EB); Department of Pharmacology and Therapeutics, University College Cork, Ireland (BMB); Cedars-Sinai Medical Center, Los Angeles, California, USA (Y-DIC, XL, JIR); Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands (AJMC, RGJW); California Pacific Medical Center Research Institute, San Francisco, CA, USA (DSE); Robertson Centre for Biostatistics, University of Glasgow, Glasgow, United Kingdom (IF); Laboratory of Epidemiology, Demography, and Biometry, Intramural Research Program, National Institute on Aging, Bethesda, Maryland, USA (MEG, TBH); Department of Medicine, University of California, San Francisco, California, USA (W-CH); Genetic Epidemiology Unit, Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands and Centre for Medical Systems Biology, Leiden, the Netherlands (AI, BAO, CMVD); Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands (BPK, ME, JAK, JCW, AH, AG, FR, BHS); Netherlands Consortium for Healthy Aging (NCHA), Leiden, The Netherlands (BPK, JCW, AH, AGU, FR, BHS); THL-National Institute for Health and Welfare, Helsinki, Finland (PK, KK, ML, VS); Department of Medical Informatics, Erasmus Medical Center, Rotterdam, The Netherlands (JAK, BHS); Department of Epidemiology and Prevention, Division of Public Health Sciences, Wake Forest University, Winston-Salem, North Carolina, USA (YL); Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom (PWM); Program in Medical and Population Genetics, Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts, USA and Center for Human Genetic Research, Cardiovascular Research Center, Harvard Medical School, and Massachusetts General Hospital, Boston, Massachusetts, USA (CN-C); Division of Cardiology, Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland (MSN, KP); National Heart Lung and Blood Institute's Framingham Heart Study, Framingham, Massachusetts, USA and Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts, USA (GMP); Icelandic Heart Association, Kopavogur, Iceland (AVS, VG); Department of Biostatistics, University of Washington, Seattle, Washington, USA (KR); BHF Glasgow Cardiovascular Research Centre, Faculty of Medicine, Glasgow, United Kingdom (Naveed Sattar); Department of Molecular Epidemiology, Leiden University Medical Center, Leiden, The Netherlands (PES); Academic Section of Geriatric Medicine, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom (DJS); Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands (ST, JWJ); Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands (AGU, FFR, BHS)

## Affiliations

Departments of Epidemiology (CLA, TS, EAW), and Medicine (EAW), the University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; Departments of Medicine (BMP), Health Services (BMP), Epidemiology (SRH, BMP, DSS) Cardiovascular Health Research Unit (CMS, SRH, BMP, DSS, JB, DE, HH) and Division of Cardiology (NS), University of Washington, Seattle, Washington, USA; Group Health Research Institute, Group Health Cooperative, Seattle, Washington, USA (BMP); Department of Epidemiology, University of Alabama Birmingham, Birmingham, Alabama, USA (DKA); McKusick-Nathans Institute of Genetic Medicine and Department of Medicine, Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA (DEA); Division of Epidemiology and Center for Human Genetics, The University of Texas Health Science Center, Houston Texas, USA (EB); Department of Pharmacology and Therapeutics, University College Cork, Ireland (BMB); Cedars-Sinai Medical Center, Los Angeles, California, USA (Y-DIC, XL, JIR); Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands (AJMC, RGJW); California Pacific Medical Center Research Institute, San Francisco, CA, USA (DSE); Robertson Centre for Biostatistics, University of Glasgow, Glasgow, United Kingdom (IF); Laboratory of Epidemiology, Demography, and Biometry, Intramural Research Program, National Institute on Aging, Bethesda, Maryland, USA (MEG, TBH); Department of Medicine, University of California, San Francisco, California, USA (W-CH); Genetic Epidemiology Unit, Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands and Centre for Medical Systems Biology, Leiden, the Netherlands (AI, BAO, CMVD); Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands (BPK, ME, JAK, JCW, AH, AG, FR, BHS); Netherlands Consortium for Healthy Aging (NCHA), Leiden, The Netherlands (BPK, JCW, AH, AGU, FR, BHS); THL-National Institute for Health and Welfare, Helsinki, Finland (PK, KK, ML, VS); Department of Medical Informatics, Erasmus Medical Center, Rotterdam, The Netherlands (JAK, BHS); Department of Epidemiology and Prevention, Division of Public Health Sciences, Wake Forest University, Winston-Salem, North Carolina, USA (YL); Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom (PWM); Program in Medical and Population Genetics, Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts, USA and Center for Human Genetic Research, Cardiovascular Research Center, Harvard Medical School, and Massachusetts General Hospital, Boston, Massachusetts, USA (CN-C); Division of Cardiology, Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland (MSN, KP); National Heart Lung and Blood Institute's Framingham Heart Study, Framingham, Massachusetts, USA and Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts, USA (GMP); Icelandic Heart Association, Kopavogur, Iceland (AVS, VG); Department of Biostatistics, University of Washington, Seattle, Washington, USA (KR); BHF Glasgow Cardiovascular Research Centre, Faculty of Medicine, Glasgow, United Kingdom (Naveed Sattar); Department of Molecular Epidemiology, Leiden University Medical Center, Leiden, The Netherlands (PES); Academic Section of Geriatric Medicine, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom (DJS); Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands (ST, JWW); Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands (AGU, FFR, BHS)

## Acknowledgments

**Atherosclerosis Risk in Communities Study (ARIC):** The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C), R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. The authors thank the staff and participants of the ARIC study for their important contributions. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research.

**Cardiovascular Health Study (CHS):** This CHS research was supported by NHLBI contracts N01-HC-85239, N01-HC-85079 through N01-HC-85086; N01-HC-35129, N01-HC-15103, N01-HC-55222, N01-HC-75150, N01-HC-45133, HHSN268201200036C and NHLBI grants HL080295, HL075366, HL087652, HL105756 with additional contribution from NINDS. Additional support was provided through AG-023629, AG-15928, AG-20098, and AG-027058 from the NIA. See also <http://www.chs-nhlbi.org/pi.htm>. DNA handling and genotyping was supported in part by National Center for Research Resources CTSI grant UL1RR033176, National Institute of Diabetes and Digestive and Kidney Diseases grant DK063491 to the Southern California Diabetes Endocrinology Research Center, and the Cedars-Sinai Board of Governors' Chair in Medical Genetics (JIR).

**Framingham Heart Study (FHS):** FHS work was supported by the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine (Contract No. N01-HC-25195), its contract with Affymetrix, Inc. for genotyping services (Contract No. N02-HL-6-4278), based upon analyses by Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project. A portion of this research was conducted using the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center. Measurement of the Gen 3 ECGs was supported by grants from the Doris Duke Charitable Foundation and the Burroughs Wellcome Fund (Newton-Cheh) and the NIH (HL080025, Newton-Cheh).

**Health 2000:** Supported by the Orion-Farmos Research Foundation (KK and KP), the Finnish Foundation for Cardiovascular Research (KK, KP), and the Academy of Finland (grant numbers 129494 and 139635 to VS).

**Health ABC:** This research was supported by NIA contracts N01AG62101, N01AG62103, and N01AG62106. The genome-wide association study was funded by NIA grant 1R01AG032098-01A1 to Wake Forest University Health Sciences and genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University, contract number HHSN268200782096C. This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging.

**MESA:** MESA and MESA SNP Health Association Resource (SHARe) are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support is provided by grants and contracts N01-HC-95159 through N01-HC-95169 and RR-024156. Funding for SHARe genotyping was provided by NHLBI Contract N02-HL-6-4278. Additional funding was supported in part by the Clinical Translational Science Institute grant UL1RR033176 and the Cedars-Sinai General Clinical Research Center grant RR00425. The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at <http://www.mesa-nhlbi.org>.

**PROSPER:** The PROSPER study was supported by an investigator initiated grant obtained from Bristol-Myers Squibb. Prof. Dr. J. W. Jukema is an Established Clinical Investigator of the Netherlands Heart Foundation (grant 2001 D 032). Support for genotyping was provided by the seventh framework program of the European commission (grant 223004) and by the Netherlands Genomics Initiative (Netherlands Consortium for Healthy Aging grant 050-060-810).

**Rotterdam Study:** The Rotterdam Study (RS) is supported by the Erasmus Medical Center and Erasmus University Rotterdam; The Netherlands Organization for Scientific Research; The Netherlands Organization for Health Research and Development (ZonMw); the Research Institute for Diseases in the Elderly; The Netherlands Heart Foundation; the Ministry of Education, Culture and Science; the Ministry of Health Welfare and Sports; the European Commission; and the Municipality of Rotterdam. Support for genotyping was provided by The Netherlands Organization for Scientific Research (NWO) (175.010.2005.011, 911.03.012) and Research Institute for Diseases in the Elderly (RIDE). This study was supported by The Netherlands Genomics Initiative (NGI)/Netherlands Organization for Scientific Research (NWO) project nr. 050-060-810.

This collaborative effort was supported by an award from the National Heart, Lung, and Blood Institute (R01-HL-103612, PI BMP).

CLA was supported in part by grant R00-HL-098458 from the National Heart, Lung, and Blood Institute

## References

1. Mancinelli L, Cronin M, Sadee W. Pharmacogenomics: the promise of personalized medicine. *AAPS PharmSci*. 2000; 2(1):E4. [PubMed: 11741220]
2. Weinshilboum R. Inheritance and drug response. *The New England journal of medicine*. 2003; 348(6):529–537. [PubMed: 12571261]
3. Phillips KA, Veenstra DL, Oren E, Lee JK, Sadee W. Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review. *JAMA : the journal of the American Medical Association*. 2001; 286(18):2270–2279. [PubMed: 11710893]
4. Wilke RA, Dolan ME. Genetics and variable drug response. *JAMA : the journal of the American Medical Association*. 2011; 306(3):306–307. [PubMed: 21771992]
5. Aithal GP, Day CP, Kesteven PJ, Daly AK. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. *Lancet*. 1999; 353(9154):717–719. [PubMed: 10073515]
6. Rettie AE, Wienkers LC, Gonzalez FJ, Trager WF, Korzekwa KR. Impaired (S)-warfarin metabolism catalysed by the R144C allelic variant of CYP2C9. *Pharmacogenetics*. 1994; 4(1):39–42. [PubMed: 8004131]
7. Fellay J, Thompson AJ, Ge D, Gumbs CE, Urban TJ, Shianna KV, et al. ITPA gene variants protect against anaemia in patients treated for chronic hepatitis C. *Nature*. 2010; 464(7287):405–408. [PubMed: 20173735]
8. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *The New England journal of medicine*. 2004; 351(27):2817–2826. [PubMed: 15591335]
9. Roden DM, Wilke RA, Kroemer HK, Stein CM. Pharmacogenomics: the genetics of variable drug responses. *Circulation*. 2011; 123(15):1661–1670. [PubMed: 21502584]
10. Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, et al. Finding the missing heritability of complex diseases. *Nature*. 2009; 461(7265):747–753. [PubMed: 19812666]
11. Daly AK. Genome-wide association studies in pharmacogenomics. *Nature reviews Genetics*. 2010; 11(4):241–246.
12. Vaidean GD, Schroeder EB, Whitsel EA, Prineas RJ, Chambless LE, Perhac JS, et al. Short-term repeatability of electrocardiographic spatial T-wave axis and QT interval. *Journal of electrocardiology*. 2005; 38(2):139–147. [PubMed: 15892024]
13. Hanson B, Tuna N, Bouchard T, Heston L, Eckert E, Lykken D, et al. Genetic factors in the electrocardiogram and heart rate of twins reared apart and together. *The American journal of cardiology*. 1989; 63(9):606–609. [PubMed: 2919564]
14. Newton-Cheh C, Larson MG, Corey DC, Benjamin EJ, Herbert AG, Levy D, et al. QT interval is a heritable quantitative trait with evidence of linkage to chromosome 3 in a genome-wide linkage analysis: The Framingham Heart Study. *Heart rhythm : the official journal of the Heart Rhythm Society*. 2005; 2(3):277–284. [PubMed: 15851319]
15. Pratt CM, Ruberg S, Morganroth J, McNutt B, Woodward J, Harris S, et al. Dose-response relation between terfenadine (Seldane) and the QTc interval on the scalar electrocardiogram: distinguishing a drug effect from spontaneous variability. *American heart journal*. 1996; 131(3):472–480. [PubMed: 8604626]
16. Roden DM. Drug-induced prolongation of the QT interval. *The New England journal of medicine*. 2004; 350(10):1013–1022. [PubMed: 14999113]
17. Moss AJ. The QT interval and torsade de pointes. *Drug safety : an international journal of medical toxicology and drug experience*. 1999; 21(Suppl 1):5–10. discussion 81–17. [PubMed: 10597863]
18. Dekker JM, Crow RS, Hannan PJ, Schouten EG, Folsom AR. Heart rate-corrected QT interval prolongation predicts risk of coronary heart disease in black and white middle-aged men and women: the ARIC study. *Journal of the American College of Cardiology*. 2004; 43(4):565–571. [PubMed: 14975464]

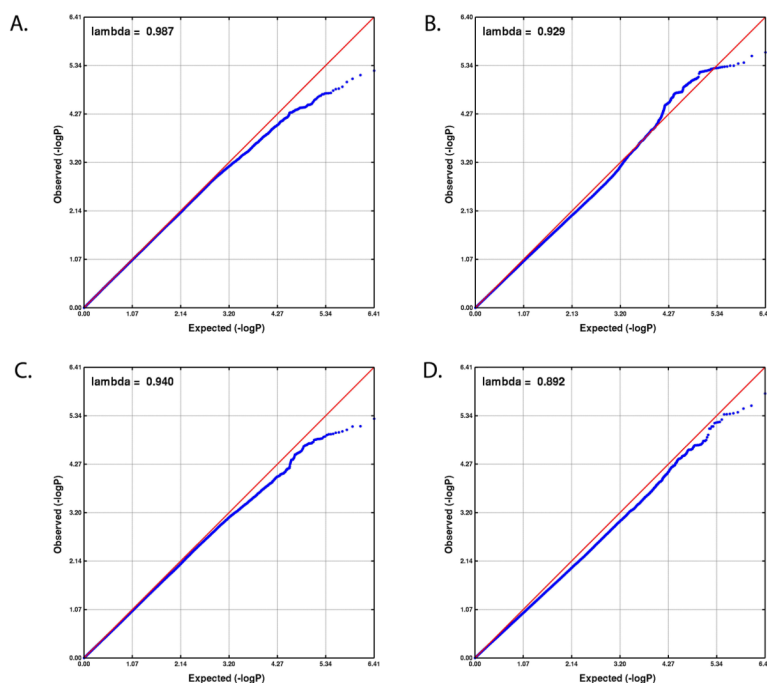
19. Zhang Y, Post WS, Blasco-Colmenares E, Dalal D, Tomaselli GF, Guallar E. Electrocardiographic QT interval and mortality: a meta-analysis. *Epidemiology*. 2011; 22(5):660–670. [PubMed: 21709561]
20. Zhang Y, Post WS, Dalal D, Blasco-Colmenares E, Tomaselli GF, Guallar E. QT-interval duration and mortality rate: results from the Third National Health and Nutrition Examination Survey. *Archives of internal medicine*. 2011; 171(19):1727–1733. [PubMed: 22025428]
21. Jamshidi Y, Nolte IM, Spector TD, Snieder H. Novel genes for QTc interval. How much heritability is explained, and how much is left to find? *Genome Med*. 2010; 2 (5):35. [PubMed: 20519034]
22. Arking DE, Pfeufer A, Post W, Kao WH, Newton-Cheh C, Ikeda M, et al. A common genetic variant in the NOS1 regulator NOS1AP modulates cardiac repolarization. *Nat Genet*. 2006; 38(6): 644–651. [PubMed: 16648850]
23. Marroni F, Pfeufer A, Aulchenko YS, Franklin CS, Isaacs A, Pichler I, et al. A genome-wide association scan of RR and QT interval duration in 3 European genetically isolated populations: the EUROSPAN project. *Circulation Cardiovascular genetics*. 2009; 2(4):322–328. [PubMed: 20031603]
24. Newton-Cheh C, Eijgelsheim M, Rice KM, de Bakker PI, Yin X, Estrada K, et al. Common variants at ten loci influence QT interval duration in the QTGEN Study. *Nature genetics*. 2009; 41(4):399–406. [PubMed: 19305408]
25. Nolte IM, Wallace C, Newhouse SJ, Waggott D, Fu J, Soranzo N, et al. Common genetic variation near the phospholamban gene is associated with cardiac repolarisation: meta-analysis of three genome-wide association studies. *PloS one*. 2009; 4(7):e6138. [PubMed: 19587794]
26. Pfeufer A, Sanna S, Arking DE, Muller M, Gateva V, Fuchsberger C, et al. Common variants at ten loci modulate the QT interval duration in the QTSCD Study. *Nature genetics*. 2009; 41(4): 407–414. [PubMed: 19305409]
27. Chambers JC, Zhao J, Terracciano CM, Bezzina CR, Zhang W, Kaba R, et al. Genetic variation in SCN10A influences cardiac conduction. *Nature genetics*. 2010; 42(2):149–152. [PubMed: 20062061]
28. Arizona Center for Education and Research on Therapeutics. Drugs that prolong the QT interval. 2011.
29. Meinert CL, Knatterud GL, Prout TE, Klimt CR. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. *Diabetes*. 1970; 19(Suppl):789–830. [PubMed: 4926376]
30. Multiple Risk Factor Intervention Trial Research Group. Baseline rest electrocardiographic abnormalities, antihypertensive treatment, and mortality in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. *The American journal of cardiology*. 1985; 55(1):1–15. [PubMed: 3880997]
31. Vieweg WV, Wood MA. Tricyclic antidepressants, QT interval prolongation, and torsade de pointes. *Psychosomatics*. 2004; 45(5):371–377. [PubMed: 15345781]
32. Rautaharju PM, Manolio TA, Psaty BM, Borhani NO, Furberg CD. Correlates of QT prolongation in older adults (the Cardiovascular Health Study). Cardiovascular Health Study Collaborative Research Group. *The American journal of cardiology*. 1994; 73(13):999–1002. [PubMed: 8184870]
33. Psaty BM, O'Donnell CJ, Gudnason V, Lunetta KL, Folsom AR, Rotter JJ, et al. Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium: Design of prospective meta-analyses of genome-wide association studies from 5 cohorts. *Circulation Cardiovascular genetics*. 2009; 2(1):73–80. [PubMed: 20031568]
34. Servin B, Stephens M. Imputation-based analysis of association studies: candidate regions and quantitative traits. *PLoS genetics*. 2007; 3(7):e114. [PubMed: 17676998]
35. Li Y, Willer CJ, Ding J, Scheet P, Abecasis GR. MaCH: using sequence and genotype data to estimate haplotypes and unobserved genotypes. *Genet Epidemiol*. 2010; 34(8):816–834. [PubMed: 21058334]
36. Nothnagel M, Ellinghaus D, Schreiber S, Krawczak M, Franke A. A comprehensive evaluation of SNP genotype imputation. *Hum Genet*. 2009; 125(2):163–171. [PubMed: 19089453]



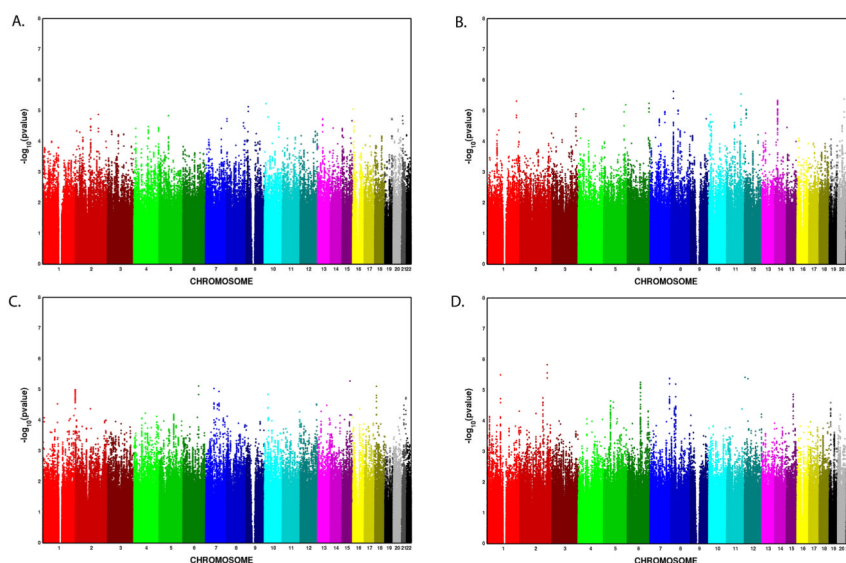
37. Der J, Avery CL, Whitsel EA, Stürmer T. Detection and Characterization of Pharmacogenomic Effects in Nonrandomized Studies - A Simulation Study of QT-Prolonging Drug-Gene Interactions. *Pharmacoepidemiol Drug Saf.* 2011; 20:S7.
38. Chen MH, Yang Q. GWAF: an R package for genome-wide association analyses with family data. *Bioinformatics.* 2010; 26(4):580–581. [PubMed: 20040588]
39. Aulchenko YS, Ripke S, Isaacs A, van Duijn CM. GenABEL: an R library for genome-wide association analysis. *Bioinformatics.* 2007; 23(10):1294–1296. [PubMed: 17384015]
40. Aulchenko YS, Struchalin MV, van Duijn CM. ProbABEL package for genome-wide association analysis of imputed data. *BMC Bioinformatics.* 2010; 11:134. [PubMed: 20233392]
41. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics.* 2010; 26(17):2190–2191. [PubMed: 20616382]
42. Devlin B, Roeder K. Genomic control for association studies. *Biometrics.* 1999; 55 (4):997–1004. [PubMed: 11315092]
43. Aberg K, Adkins DE, Liu Y, McClay JL, Bukszar J, Jia P, et al. Genome-wide association study of antipsychotic-induced QTc interval prolongation. *The pharmacogenomics journal.* 2012; 12(2): 165–172. [PubMed: 20921969]
44. Volpi S, Heaton C, Mack K, Hamilton JB, Lannan R, Wolfgang CD, et al. Whole genome association study identifies polymorphisms associated with QT prolongation during iloperidone treatment of schizophrenia. *Molecular psychiatry.* 2009; 14(11):1024–1031. [PubMed: 18521091]
45. van Noord C, Aarnoudse AJ, Eijgelsheim M, Sturkenboom MC, Straus SM, Hofman A, et al. Calcium channel blockers, NOS1AP, and heart-rate-corrected QT prolongation. *Pharmacogenetics and genomics.* 2009; 19(4):260–266. [PubMed: 19247217]
46. Jamshidi Y, Nolte IM, Dalageorgou C, Zheng D, Johnson T, Bastiaenen R, et al. Common variation in the NOS1AP gene is associated with drug-induced QT prolongation and ventricular arrhythmia. *Journal of the American College of Cardiology.* 2012; 60(9):841–850. [PubMed: 22682551]
47. Kaab S, Crawford DC, Sinner MF, Behr ER, Kannankeril PJ, Wilde AA, et al. A large candidate gene survey identifies the KCNE1 D85N polymorphism as a possible modulator of drug-induced torsades de pointes. *Circulation Cardiovascular genetics.* 2012; 5(1):91–99. [PubMed: 22100668]
48. Gu, Q.; Dillon, CF.; Burt, VL. NCHS Data Brief. National Center for Health Statistics; Hyattsville, MD: 2010. Prescription Drug Use Continues to Increase: U.S. Prescription Drug Data for 2007–2008.
49. The Foundation for Pharmaceutical Statistics. Facts and Figures 2010. In: Griens, AMGF.; Lukaart, JS.; van der Vaart, RJ., editors. 2009 in numbers. The Foundation for Pharmaceutical Statistics; The Hague, The Netherlands: 2011.
50. Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature.* 2009; 461(7262):399–401. [PubMed: 19684573]
51. Suppiah V, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, et al. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. *Nature genetics.* 2009; 41(10):1100–1104. [PubMed: 19749758]
52. Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nature genetics.* 2009; 41(10):1105–1109. [PubMed: 19749757]
53. Cooper GM, Johnson JA, Langae TY, Feng H, Stanaway IB, Schwarz UI, et al. A genome-wide scan for common genetic variants with a large influence on warfarin maintenance dose. *Blood.* 2008; 112(4):1022–1027. [PubMed: 18535201]
54. Takeuchi F, McGinnis R, Bourgeois S, Barnes C, Eriksson N, Soranzo N, et al. A genome-wide association study confirms VKORC1, CYP2C9, and CYP4F2 as principal genetic determinants of warfarin dose. *PLoS genetics.* 2009; 5(3):e1000433. [PubMed: 19300499]
55. Link E, Parish S, Armitage J, Bowman L, Heath S, Matsuda F, et al. SLCO1B1 variants and statin-induced myopathy--a genomewide study. *The New England journal of medicine.* 2008; 359(8): 789–799. [PubMed: 18650507]



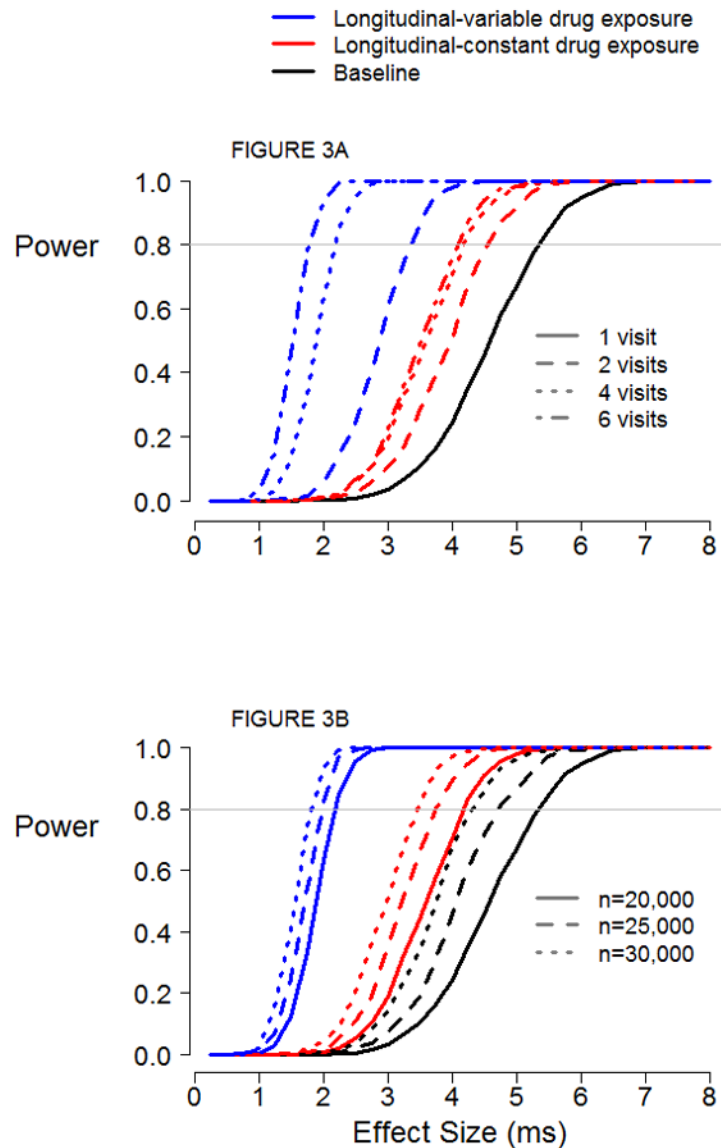
56. Smith NL, Psaty BM, Heckbert SR, Tracy RP, Cornell ES. The reliability of medication inventory methods compared to serum levels of cardiovascular drugs in the elderly. *Journal of clinical epidemiology*. 1999; 52(2):143–146. [PubMed: 10201655]
57. Qato DM, Schumm LP, Johnson M, Mihai A, Lindau ST. Medication data collection and coding in a home-based survey of older adults. *J Gerontol B Psychol Sci Soc Sci*. 2009; 64 (Suppl 1):i86–93. [PubMed: 19491196]
58. Wong MY, Day NE, Luan JA, Chan KP, Wareham NJ. The detection of gene-environment interaction for continuous traits: should we deal with measurement error by bigger studies or better measurement? *Int J Epidemiol*. 2003; 32(1):51–57. [PubMed: 12690008]
59. Nettleton JA, McKeown NM, Kanoni S, Lemaitre RN, Hivert MF, Ngwa J, et al. Interactions of dietary whole-grain intake with fasting glucose- and insulin-related genetic loci in individuals of European descent: a meta-analysis of 14 cohort studies. *Diabetes care*. 2010; 33(12):2684–2691. [PubMed: 20693352]
60. Beardon PH, McGilchrist MM, McKendrick AD, McDevitt DG, MacDonald TM. Primary non-compliance with prescribed medication in primary care. *BMJ*. 1993; 307(6908):846–848. [PubMed: 8401129]
61. Sanguinetti MC, Jiang C, Curran ME, Keating MT. A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the IKr potassium channel. *Cell*. 1995; 81(2):299–307. [PubMed: 7736582]

**FIGURE 1.**

Quantile-quantile (Q-Q) plots of drug-SNP interaction estimates after meta-analysis of summary results from ten cohorts of European descent. Drug classes are as follows: panel A, thiazide diuretics; panel B, sulfonylurea hypoglycemic agents; panel C, University of Arizona Center for Education and Research on Therapeutics (UAZ CERT)-classified QT prolonging drugs; panel D, tri/tetracyclic antidepressants.

**FIGURE 2.**

Manhattan plots of drug-SNP interaction estimates after meta-analysis of summary results from ten cohorts of European descent. Drug classes are as follows: panel A, thiazide diuretics; panel B, sulfonylurea hypoglycemic agents; panel C, University of Arizona Center for Education and Research on Therapeutics (UAZ CERT)-classified QT prolonging drugs; panel D, tri/tetracyclic antidepressants.

**FIGURE 3.**

Statistical power of a simulated pharmacogenomics study of QT. The following assumptions were used for the calculations; 2–6 serial visits measuring ECGs and drug exposure,  $n=20,000$ – $30,000$  participants, a SNP minor allele frequency of 0.20, and the prevalence of drug exposure at any one visit of 10%. The solid black lines represent a cross-sectional analysis, the red lines a longitudinal model evaluating drug exposure measured at baseline and repeated ECG measures, and the blue lines a longitudinal model with drug exposure and ECG assessed at all visits. Figure 3A assumes 20,000 participants, with variable number of visits. Figure 3B assumes four visits, with a variable number of participants.

**TABLE 1**  
Baseline characteristics of ten cohorts examining pharmacogenomic effects on the QT interval.

Cohort	N <sup>†</sup>	QT (ms)	Age (years)	Female	Prevalence of Drug Exposure			UAZ CERT <sup>‡</sup>
					Thiazides	Sulfonylureas	TCAs	
AGES	2,587	406 (35)	76 (5)	1,606 (62.1)	624 (24.1)	62 (3.1)	95 (4.8)	147 (7.3)
ARIC	8,132	398 (28)	54 (6)	4,279 (52.6)	951 (11.7)	152 (1.9)	227 (2.8)	360 (4.5)
CHS	2,813	414 (32)	72 (5)	1,760 (62.5)	582 (20.7)	110 (3.9)	94 (3.2)	143 (5.1)
ERF	1,503	398 (28)	48 (14)	887 (59.0)	29 (2.0)			49 (3.3)
FHS	3,168	414 (30)	40 (9)	1,920 (60.0)	89 (2.8)	23 (0.83)	56 (1.8)	132 (4.8)
Health ABC	1,435	413 (36)	74 (3)	709 (49.4)	218 (11.1)	81 (6.2)	43 (3.0)	108 (8.2)
Health 2000	2,124	389 (30)	50 (11)	1,104 (52.0)	104 (7.2)			27 (1.3)
MESA	2,217	412 (29)	62 (10)	1,156 (52.1)	281 (12.7)	55 (2.4)	44 (1.9)	104 (4.6)
PROSPER	4,556	414 (36)	75 (3)	2,445 (54.0)	1,175 (25.8)	243 (4.9)	151 (3.3)	281 (5.7)
RS1	3,647	397 (28)	68 (8)	2,184(59.9)	251 (6.9)	95 (2.5)	38 (1.0)	105 (2.8)
RS2	1,599	402 (28)	64 (8)	890 (55.7)	92 (5.8)	48 (3.1)	24 (1.5)	47 (3.0)
<b>Summary:</b>	<b>33,781</b>	<b>Range: 389, 414</b>	<b>Range: 40, 75</b>	<b>Range: 49.4, 62.5%</b>	<b>4,396 (13.0)</b>	<b>869 (2.9)</b>	<b>772 (2.6)</b>	<b>1,503 (4.4)</b>

\* Data presented as mean (standard deviation) or N (proportion).

<sup>†</sup> Number of participants varied by analysis. Number of participants meeting common exclusion criteria presented.

<sup>‡</sup> Included drugs classified as definite and possible QT prolonging agents. AGES, Age, Gene/Environment Susceptibility – Reykjavik Study. ARIC, Atherosclerosis Risk in Communities study. CHS, Cardiovascular Health Study. ERF, Erasmus Rucphen Family study. FHS, Framingham Heart Study. Health ABC, Health Aging, Body and Composition. MESA, Multi-Ethnic Study of Atherosclerosis. MS, milliseconds. N, number. PROSPER, Prospective Study of Pravastatin in the Elderly at Risk. RS, Rotterdam Study. SNP, single nucleotide polymorphism. TCA, tri-/tetra-cyclic antidepressants. UAZ CERT, University of Arizona Center for Education and Research on Therapeutics QT prolonging agents classification.

t-distribution meta-analytic *P*-values from ten cohorts examining drug-SNP interactions limited to 26 SNPs with genome-wide significant effects reported in prior studies of the QT-SNP association among populations of European descent.

TABLE 2

Previously identified locus*	European index SNP	Alleles <sup>†</sup>	CAF	Interaction <i>P</i> -value <sup>‡</sup>			
				Thiazides	Sulfonylureas	UAZ CERT	TCAs
<i>RNF207</i>	rs846111 <sup>24, 26</sup>	C/G	0.28	0.90	0.43	0.67	0.02
	rs12143842 <sup>24-26</sup>	T/C	0.25	0.60	0.85	0.11	0.40
<i>NOS1AP</i>	rs12029454 <sup>24</sup>	A/G	0.15	0.10	0.26	0.87	0.66
	rs16857031 <sup>24</sup>	C/G	0.87	0.01	0.96	0.98	0.85
	rs4657178 <sup>26</sup>	T/C	0.25	0.52	0.76	0.15	0.78
	rs2880058 <sup>23, 27</sup>	A/G	0.67	0.84	0.36	0.56	0.62
<i>ATP1B1</i>	rs10494366 <sup>22</sup>	T/G	0.64	0.35	0.93	0.25	0.74
	rs10919071 <sup>26</sup>	A/G	0.87	0.92	0.68	0.66	0.73
<i>SCN5A</i>	rs12053903 <sup>24</sup>	T/C	0.68	0.32	0.18	0.93	0.74
	rs11129795 <sup>26</sup>	A/G	0.24	0.09	0.26	0.95	0.57
<i>PLN, SLC35F1</i>	rs11756438 <sup>24</sup>	A/C	0.48	0.90	0.36	0.24	0.74
	rs11153730 <sup>25</sup>	T/C	0.50	0.64	0.20	0.80	0.72
<i>KCNH2</i>	rs11970286 <sup>26</sup>	T/C	0.47	0.39	0.63	0.70	0.73
	rs12210810 <sup>26</sup>	C/G	0.06	0.70	0.65	0.28	0.70
	rs4725982 <sup>24</sup>	T/C	0.22	0.76	0.65	0.28	0.75
	rs2968864 <sup>24</sup>	T/C	0.76	0.62	0.59	0.44	0.11
<i>KCNQ1</i>	rs2968863 <sup>26</sup>	T/C	0.24	0.58	0.84	0.17	0.11
	rs2074238 <sup>24</sup>	T/C	0.06	0.02	0.90	0.18	0.67
Intergenic	rs12576239 <sup>24</sup>	T/C	0.13	0.05	0.16	0.98	0.34
	rs12296050 <sup>26</sup>	T/C	0.18	0.03	0.12	0.64	0.77
<i>LITAF</i>	rs2478333 <sup>23</sup>	A/C	0.36	0.35	0.15	0.10	0.22
<i>NDRG4</i>	rs8049607 <sup>24, 26</sup>	T/C	0.50	0.01	0.55	0.03	0.20
	rs7188697 <sup>26</sup>	A/G	0.74	0.36	0.39	0.79	0.62
<i>LIG3, RFFL</i>	rs37062 <sup>24</sup>	A/G	0.75	0.49	0.39	0.23	0.63
	rs2074518 <sup>24</sup>	T/C	0.46	0.29	0.35	0.33	0.86



Previously identified locus <sup>*</sup>	European index SNP	Alleles <sup>†</sup>	CAF	Interaction <i>P</i> -value <sup>‡</sup>		
				Thiazides	Sulfonylureas	UAZ CERT TCAs
<i>KCNJ2</i>	rs17779747 <sup>26</sup>	T/G	0.33	0.50	0.90	0.85 0.18

<sup>\*</sup> All SNPs reported in genome-wide literature are examined. No linkage disequilibrium filter was applied.

<sup>†</sup> Coded allele listed first.

<sup>‡</sup> Meta-analysis was performed on interaction *P*-values. CAF, coded allele frequency. SNP, single nucleotide polymorphism. TCA, tri-/tetra-cyclic antidepressants. UAZ CERT, University of Arizona Center for Education and Research on Therapeutics QT prolonging agents classification.